REMARKS

I. Overview

Applicants have reviewed and considered the Office Action dated November 29, 2004 and the reference cited therewith. Applicants note the withdrawal of the 35 U.S.C. § 102(b) rejection to claims 26-27, 29, 31, 35, and 39. Claims 19-27, 29, 31-33 and 35-39 are pending in the current application. Claims 19, 24, 26, 31, and 32 have been amended. Support for these amendments can be found at pages 13, 15-17, and 37 in the Specification. Claims 22-23, 27, 29, 33, and 35-39 have been canceled. Applicants respectfully request reconsideration of the above-identified application in view of the amendments above and the remarks that follow.

II. Claim Rejections - 35 U.S.C. § 102

Claims 19-25, 32-33 and 36-38 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Link et al., (1996) Human Gene Therapy, Vol. 7, 1161-1179. The Examiner states that contrary to Applicants' interpretation of the amendment, the claims do not preclude subsequent administration of ganciclovir.

The Examiner states that the Applicants appear to be arguing that since the Link et al. reference did not recognize that hyperacute rejection can mediate tumor killing through complement, Link et al. cannot anticipate the instant claims. It is respectfully submitted that the Examiner appears to misunderstand the invention. Link et al. refers to a chemotherapeutic bystander effect mediated by ganciclovir diffusion while the claims in the present invention refer to immune therapeutic bystander effect initiated by a hyperacute response to xenogeneic cells when injected into or near a solid tumor. The anti-tumor immune response referred to in Link et

al. is not mediated by a hyperacute response. Link et al. is merely referencing experiments performed in rats and mice with murine VPCs, which do not trigger hyperacute responses.

The Examiner refers to the previous Office Action and reiterates that the ability of murine VPCs to induce hyperacute rejection in humans is inherent property due to the fact that murine cells naturally express alpha (1,3) galactosyl epitopes and the fact that humans possess preformed anti-xenogeneic antibodies. The Examiner states that Link et al. teach the same method steps as those recited in the claims, using the same VPCs as disclosed by the Applicants, therefore Link et al. anticipates the claims as written. Applicants have amended independent claims 19, 26 and 32 to specifically indicate that ganciclovir is not administered.

Amended claim 19 recites a method for treating a solid tumor "and not administering ganciclovir." Thus, the Link et al does not teach each element of claim 19, specifically where treatment of a solid tumor is not followed by treatment with ganciclovir, because the method in Link et al, rather than Applicants' method, treats a tumor using a chemotherapeutic bystander effect mediated by ganciclovir diffusion. Therefore, claim 19 is not anticipated by Link et al. Dependent claims 20-21 and 24-25 recite similar elements as claim 19 and are patentable over Link for similar reasons as those argued above, plus the elements in the claims. Independent claims 26 and 32 have been similarly amended to note "wherein administration of said vector producing cells to said subject is not followed by treatment with ganciclovir" and are patentable over Link for similar reasons as those argued above, plus the elements in the claims. Dependent claim 31 recites similar elements as claim 26 is patentable over Link for similar reasons as those argued above, plus the elements in the claims. In light of the above, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn and reconsidered.

III. Claim Rejections - 35 U.S.C. § 112

The Examiner states that claims 19-27, 29, 31-33, and 35-39 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for methods of inhibiting the growth of a solid tumor in a human subject comprising administering at or near a solid tumor on an effective amount of xenogeneic retroviral vector producer cells having alpha (1,3) galactosyl epitopes, wherein said amount activates a hyperacute rejection response against said xenogeneic cells and an innocent bystander immune response against tumor cells, thereby inhibiting the growth of the tumor in the human subject with or without the subsequent administration of ganciclovir, does not reasonably provide enablement for methods for treating non-solid tumors by administering xenogeneic cells or methods of treating solid tumors comprising administering xenogeneic cells which are not vector producing cells to any site in the subject.

The Examiner states that as such, the skilled artisan would not have been able to predict without undue experimentation whether the administration of murine cells or other xenogeneic cells expressing gal epitopes which are not vector producing cells would be capable of stimulating sufficient immune response such that innocent bystander immune responses against the tumor would occur and would result in treatment of the tumor. Applicants disagree, however, in an effort to expedite prosecution have amended the claims to vector producer cells.

Claim 19 as amended now recites, "a method for treating a solid tumor in a human subject, the method comprising: administering to the subject at or near the solid tumor an effective amount of xenogeneic retroviral vector producer cells having alpha (1,3) galactosyl epitopes to active a hyperacute rejection response . . . ." Support for this amendment can be

found in the Specification at page 16. Independent claims 26 and 32 have been similarly amended. Claims 22-23, 27, 29, 33, and 35-39 have been cancelled.

The Examiner states that the VPCs produce retrovirus capable of infecting the neighboring tumor cells, it is therefore unclear whether the anti-tumor responses observed are the result of anti-retroviral immune responses, hyperacute immune responses against the gal epitopes on the murine VPCs leading to innocent bystander killing of the tumor cells, or a combination of the two.

Applicants respectfully disagree with the Examiner. The retroviruses that are produced by the cells in the instant invention do not encode any retroviral protein. The vector that is produced by these cells contains a stop code on at the gag initiation codon and it does not produce even a truncated fragment of a retroviral protein. Furthermore, even if they did, the efficiency of gene transfer of less than 0.1% would not justify such a strong anti-tumor immune reaction as was observed in the patient.

The Examiner states that the specification clearly teaches that the immune responses against the tumor are "innocent bystander immune responses". The Examiner states that the disclosed methods do not generate specific anti-tumor immune responses, rather the immune responses generated against the xenogeneic antigens and/or retroviral antigens expressed by the xenogeneic cells are capable of non-specifically killing other cells in the vicinity of the xenogeneic cells.

Applicants disagree with the Examiner's statement. There are two events that have to be recognized and distinguished here. The first event relates to how an immune response is triggered – stimulation, and the second event relates to the recognition of target cells by the immune cells - effecter. It is wrong to say that an innocent bystander immune response does not

involve a specific anti-tumor immune response. The anti-tumor response is triggered by collaterally damaged tumor cells at the site of injection of the xenogeneic cells instead of by the tumor cells alone in the absence of additional stimulation. The resulting anti-tumor immune response is specific to the tumor. Example 13 in the specification, at pages 37, reports data of anti-tumor immune response that shows increased levels of eosiniphils on day 7 and 14 after VPC injection, increased levels of IL-5 in peritoneal fluid from treated patients.

Applicants strongly disagree with Examiner's statement that neither the art at the time of filing, nor the specification or declaration, provide any evidence that the administration of xenogeneic cells or xenogeneic VPCs result in systemic non-specific killing of cells, or the non-specific killing of any particular cell type distant from the site of xenogeneic cell administration. Applicants respectfully submit that this argument and conclusion are simply wrong as the Examiner is forgetting to consider the strong and systematic immune suppression mechanism that control auto-immune destruction of normal tissue. In light of the above, Applicants submit that amended claims 19-21, 24-26, and 31-32 are fully enabling and commensurate in scope with the disclosure of the claimed invention. Therefore, Applicants request that the rejections under 35 USC §112 be withdrawn and reconsidered.

IV. Conclusion

This is a request to extend the period for filing a response in the above-identified application for one month from February 28, 2005 to March 28, 2005. Applicant is a small entity; therefore, please charge Deposit Account number 26-0084 in the amount of $60.00 to cover the cost of the one month extension. Any deficiency or overpayment should be charged or credited to Deposit Account 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

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